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Functional Recovery After Coronary Revascularization for Chronic Coronary Artery Disease Is Dependent on Maintenance of Oxidative Metabolism

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Objectives. **This study was performed to define the importance of maintenance of oxidative metabolism as a descriptor and determinant of functional recovery after revascularization in patients with left ventricular dysfunction attributable to chronic coronary artery disease.**

Background. **Although myocardial accumulation of ^{18}F-fluorodeoxyglucose indicates the presence of tissue that is metabolically active, it may not identify those metabolic processes required for restoration of myocardial contractility. Experimental studies suggest that, under conditions of ischemia and reperfusion, maintenance of myocardial oxidative metabolism is an important metabolic determinant of the capacity for functional recovery.**

Methods. **In 16 patients positron emission tomography was performed to characterize myocardial perfusion (with $H_2{}^{15}O$), oxidative metabolism (with ^{11}C-acetate) and utilization of glucose (with ^{18}F-fluorodeoxyglucose). Dysfunctional but viable myocardium was differentiated from nonviable myocardium on the basis of assessments of regional function before and after coronary revascularization. To define the importance of coronary revascularization on myocardial perfusion and metabolism, tomography was repeated in 11 patients after revascularization.**

Results. **Before revascularization, perfusion in 24 dysfunctional but viable myocardial segments and 29 nonviable segments averaged 79% and 74%, respectively, of that in 42 normal myocardial segments (both $p < 0.01$). Dysfunctional but viable myocardium exhibited oxidative metabolism comparable to that in normal myocardium. In contrast, in nonviable myocardium, oxidative metabolism was only 66% of that in normal ($p < 0.01$) and 69% of that in reversibly dysfunctional myocardium ($p < 0.003$). Regional utilization of glucose normalized to regional perfusion in dysfunctional but viable myocardium was greater than that in normal myocardium ($p < 0.01$). However, in both reversibly and persistently dysfunctional myocardium, utilization of glucose normalized to relative perfusion was markedly variable.**

Conclusions. **The results indicate that preservation of oxidative metabolism is a necessary condition for recovery of function after coronary recanalization in patients with chronic coronary artery disease. Consequently, approaches that measure myocardial oxygen consumption, such as dynamic positron emission tomography with ^{11}C-acetate, should facilitate the identification of those patients most likely to benefit from coronary revascularization.**

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The primary objective in restoring nutritive perfusion to mechanically dysfunctional myocardium in patients with chronic coronary artery disease is to improve the contractile performance of the heart. From a clinical standpoint, when dysfunctional myocardium retains the capacity for functional recovery, it is generally considered to be viable. Conversely, tissue that lacks the capacity for functional recovery is considered to be nonviable (1). Consequently, the optimal selection of patients with left ventricular dysfunction attributable to chronic coronary artery disease who can benefit most from revascularization requires accurate differentiation of dysfunctional but viable myocardium from nonviable myocardium.

Because depressed regional contractile performance secondary to ischemia generally reflects underlying derangements of myocardial metabolism, characterization of altered myocardial metabolism with positron emission tomography is a promising approach for detecting dysfunctional but still viable myocardium. Metabolism of glucose (anaerobic and aerobic) predominates in ischemic as opposed to well oxy-

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genated normal myocardium. Thus, positron emission tomography with ^{18}F-fluorodeoxyglucose has been proposed as a means to delineate viable from nonviable myocardium in patients with coronary artery disease (2,3). In patients with left ventricular dysfunction attributable to chronic coronary artery disease, persistence of myocardial utilization of glucose (reflected by the myocardial accumulation of ^{18}F-fluorodeoxyglucose) has been shown to be predictive of a restoration of function after revascularization whether or not hypoperfusion was present initially. However, positron emission tomography with ^{18}F-fluorodeoxyglucose falsely predicts tissue viability in approximately 15% to 22% of all cases and tissue nonviability 8% to 22% of the time (2,3). A potential explanation for the discordance is that myocardial accumulation of ^{18}F-fluorodeoxyglucose indicates the presence of tissue that is metabolically active but does not identify specific metabolic processes required for restoration of myocardial contractility. Consequently, approaches that specifically delineate these metabolic processes might prove more accurate in identifying dysfunctional but viable myocardium.

Under physiologic conditions, myocardial oxidative metabolism is a prerequisite for contractile function (4,5). Results of studies (6–8) with isolated heart preparations and in laboratory animals and patients with recent myocardial infarction have demonstrated that maintenance of oxidative metabolism in ischemic myocardium and its enhancement after recanalization are likely to be the critical determinants of ultimate recovery of contractile performance. Analogous data are not yet available from studies of human subjects with more chronic coronary syndromes. Accordingly, the present study was performed to define the importance of maintenance of oxidative metabolism as a descriptor and determinant of the potential for functional recovery after revascularization in patients with left ventricular dysfunction attributable to chronic coronary artery disease. Positron emission tomography was performed to characterize myocardial perfusion (with $H_2{}^{15}O$) oxidative metabolism (with ^{11}C-acetate) and utilization of glucose (with ^{18}F-fluorodeoxyglucose) in dysfunctional tissue and to differentiate viable from nonviable myocardium as verified by serial assessment of regional ventricular performance before and after coronary revascularization.

Methods

Patients studied. Sixteen patients (11 men and 5 women; mean age 59 years [range 30 to 69]) who had left ventricular wall motion abnormalities secondary to angiographically documented coronary artery disease were studied. The clinical characteristics and angiographic findings of these patients are shown in Table 1. Eleven patients had sustained at least one myocardial infarction, the most recent occurring 11 days before the initial tomographic study. Because the kinetics of ^{18}F-fluorodeoxyglucose in the heart of patients with diabetes mellitus have not yet been well characterized, patients with diabetes mellitus were excluded. Cardiac catheterization and selective coronary angiography followed by coronary revascularization were performed in all patients. Twelve patients underwent coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty was performed in four patients. The adequacy of revascularization was based on review of the operative reports or cardiac catheterization reports documenting the successful placement of bypass grafts to or successful balloon dilation of those coronary arteries subtending dysfunctional myocardium (see later). No patient had a myocardial infarction between the initial and follow-up tomographic and wall motion studies. The protocol was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine, and written informed consent was obtained from each subject.

Assessment of ventricular function. Regional systolic function was assessed before and after revascularization in all patients (mean time after revascularization 3.1 ± 2.2 months) (Table 1). The methodology used to assess regional systolic function was identical to that recently described (8). The echocardiograms, radionuclide ventriculograms and contrast left ventriculograms were analyzed by two observers (8,9) without knowledge of the tomographic and clinical data who calculated an average wall motion score for each segment in each study.

As judged from the analysis of wall motion, myocardium was defined as 1) normal; 2) dysfunctional but viable (initially dysfunctional segments that exhibited improvement in wall motion score by at least one full grade after revascularization); or 3) nonviable (initially dysfunctional segments that did not exhibit improvement in wall motion score after revascularization) (8). In the one patient who underwent left ventricular aneurysmectomy, only those segments that were resected were included in the analysis of dysfunctional segments. As judged from gross and microscopic confirmation of extensive transmural necrosis and scarring, they were defined as nonviable. In patients who underwent coronary bypass surgery, the interventricular septum was excluded from analysis because of potential artifact associated with inadequate indexing in this region. Tomographic estimates of perfusion and metabolism before and after myocardial revascularization were correlated with respect to indexes of myocardium categorized according to systolic function.

Tomographic assessment of perfusion and metabolism. Tomographic assessments of perfusion and metabolism were performed in all 16 patients a mean of 10 days (range 1 to 30) before coronary revascularization. The assessments of systolic function were performed within 0 to 12 days (mean 2.3) of these tomographic studies. To define the impact of myocardial revascularization on regional perfusion, oxidative metabolism and utilization of glucose, tomography was repeated in 11 patients after revascularization (mean 2.5 months; range 1.2 to 3.4). Follow-up tomographic studies were not performed in the one patient who underwent left

Table 1. Clinical Characteristics of 16 Patients

Subject	Age (yr)/ Gender	Previous MI (time since MI)	Angiographic Findings	Wall Motion Study Before/After Revascularization	Number of Segments with Wall Motion Abnormalities	Revascularization Procedure
1	67/M	Yes (11 days)	90% LAD; 90% LCx; 90% RCA	Echo/Path	2	CABG and aneurysmectomy
2	50/M	Yes (14 days)	90% LAD; 100% LCx; 100% RCA	RVG/RVG	5	CABG
3	68/F	No	80% LAD; 80% LCx; 80% RCA	Echo/Echo	3	CABG
4	44/M	Yes (30 days)	90% LCx	Echo/Echo	2	PTCA
5	60/M	Yes (>1 yr)	100% LAD; 90% LCx; 100% RCA	RVG/RVG	4	CABG
6	46/M	Yes (38 days)	90% LAD	Echo/Echo	3	PTCA
7	67/F	Yes (12 days)	95% LAD	Echo/Echo	4	PTCA
8	68/M	No	70% LAD; 80% LCx; 90% RCA	Echo/Echo	6	CABG
9	67/M	Yes (>2 yr)	100% LAD; 80% LCx	Echo/Echo	2	CABG
10	65/M	No	100% LAD; 60% LCx; 100% RCA	LVG/Echo	1	CABG
11	65/F	Yes (>10 yr)	100% LAD; 100% RCA	Echo/Echo	5	CABG
12	30/M	No	100% LAD	Echo/Echo	3	CABG
13	69/F	Yes (>4 yr)	90% LAD	Echo/Echo	2	PTCA
14	64/M	Yes (>2 yr)	90% LAD; 100% LCx; 100% RCA	Echo/Echo	3	CABG
15	52/M	No	100% LAD; 100% LCx; 70% RCA	RVG/RVG	3	CABG
16	68/F	Yes (>1 yr)	100% LAD; 100% LCx; 75% RCA	Echo/Echo	5	CABG

CABG = coronary artery bypass grafting; Echo = two-dimensional echocardiography; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVG = contrast left ventriculography; M = male; MI = myocardial infarction; Path = pathologic characterization of resected myocardium; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; RVG = radionuclide ventriculography.

ventricular aneurysmectomy (because the initially dysfunctional myocardium of interest had been resected) and in four other patients (because of logistic difficulties).

The methodology used to measure regional myocardial perfusion, oxidative metabolism and utilization has been recently reported in detail (8). In brief, tomographic studies were performed with either Super PETT I or Super PETT IIB (10,11) with subjects in the postprandial state. An initial transmission scan was obtained to correct subsequent emission scans for attenuation. Then $H_2{}^{15}O$ (0.25 to 0.30 mCi/kg body weight as an intravenous bolus), ^{15}O-carbon monoxide (40 mCi by inhalation), ^{11}C-acetate (0.25 to 0.30 mCi/kg intravenously) and ^{18}F-fluorodeoxyglucose (9 to 10 mCi intravenously) were administered consecutively, with the appropriate list-mode data collection and time delay (to allow for decay) initiated after the administration of each radiopharmaceutical. To ensure that each patient was in the same position for all data collections, position was checked with the use of a low energy laser and indelible marks were placed on the torso. The estimated radiation exposure (expressed as the effective dose equivalent) for the two complete tomographic studies (before and after revascularization) was 3.6 rems.

Myocardial blood flow was assessed as previously described (12–14) based on the images of relative perfusion that were generated by correcting the composite $H_2{}^{15}O$ reconstruction for activity emanating from the intravascular compartment with the use of the composite ^{15}O-carbon monoxide image. Myocardial oxidative metabolism was quantified by determining the myocardial turnover rate constant, k_1,

which delineates the clearance of ^{11}C activity from myocardium (after the administration of ^{11}C-acetate) and correlates closely with regional myocardial oxygen consumption (15–17). Regional myocardial utilization of glucose was assessed based on composite images of relative ^{18}F-fluorodeoxyglucose activity obtained 45 min after the administration of the tracer. Analyses of tomographic images were performed with an operator-interactive image analysis procedure developed and validated in our laboratory (8). The left ventricular myocardium was divided into the same seven anatomic segments as on the wall motion studies and $H_2{}^{15}O$ activity, k_1 and ^{18}F-fluorodeoxyglucose activity were then determined for each segment. Segmental $H_2{}^{15}O$ activity and ^{18}F-fluorodeoxyglucose activity were normalized, based on values in those segments with highest values for $H_2{}^{15}O$ and ^{18}F-fluorodeoxyglucose. In addition, myocardial utilization of glucose was normalized to blood flow within a segment by dividing normalized ^{18}F-fluorodeoxyglucose activity by normalized $H_2{}^{15}O$ activity for the same segment (18). Values for perfusion, oxidative metabolism and utilization of glucose were characterized in normal, in dysfunctional but viable and in nonviable myocardium before and after coronary revascularization.

Statistical analyses. Results for continuous variables are presented as mean value ± SD. Independent and paired sample values were subjected to analysis of variance and to *t* testing corrected for the number of comparisons with the Bonferroni method. A p value < 0.05 was considered to be significant.

Results

Segmental function. In the hearts of the 16 patients studied, 95 segments were classified: 42 as normal, 24 as dysfunctional but still viable and 29 as nonviable segments. Average wall motion scores before coronary revascularization in the two categories of dysfunctional myocardium exhibited impairment of contractile performance of similar magnitude (Fig. 1). Dysfunctional but viable myocardium manifested an average wall motion score of 2.61 ± 0.77. Nonviable myocardium exhibited an average wall motion score of 2.49 ± 0.61 (p = NS). After revascularization, dysfunctional but viable myocardium (as defined by the criteria used in this study) exhibited an average improvement in wall motion score of 1.2 compared with values before revascularization (wall motion score after revascularization averaged 1.38 ± 0.58). After revascularization, regional wall motion in nonviable myocardium did not change, as evidenced by an average wall motion score after revascularization of 2.44 ± 0.70.

Estimates of perfusion and metabolism before revascularization. The tomographic measurements of myocardial perfusion and metabolism before and after coronary revascularization are summarized in Table 2 and Figure 2. Examples are shown in Figures 3 and 4. Before revascularization, dysfunctional but viable myocardium exhibited perfusion

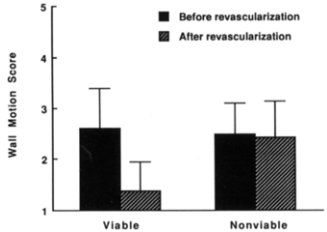

Figure 1. Histograms with average wall motion scores (and standard deviations) for segments containing viable and nonviable myocardium, before and after coronary revascularization. Before revascularization, viable and nonviable segments exhibited similar severity of mechanical dysfunction.

equivalent to 79% of that of normal myocardium ($p < 0.01$). Nonviable myocardium exhibited a similar reduction in perfusion, averaging 74% of that seen in normal myocardium ($p < 0.01$).

Dysfunctional but viable myocardium exhibited oxidative metabolism (k_1 of ^{11}C-acetate clearance) equivalent to that of normal myocardium (95% of normal, p = NS). In contrast, in nonviable myocardium, oxidative metabolism was only 66% of that in normal ($p < 0.01$) and 69% of that in reversibly dysfunctional myocardium ($p < 0.003$).

Regional ^{18}F-fluorodeoxyglucose activity was reduced to a comparable level in dysfunctional but viable and in nonviable myocardium, averaging 89% and 80% of values in normal myocardium, respectively ($p < 0.01$). Because of the likelihood of decreased count recovery secondary to partial volume effects in thinned ischemic myocardium, regional utilization of glucose was normalized to regional perfusion (a transformation that partially corrects for partial volume averaging). Dysfunctional but viable myocardium exhibited utilization of glucose normalized to relative perfusion that was 19% greater than that in normal myocardium ($p < 0.01$). However, nonviable myocardium also exhibited an apparent (but not statistically significant) augmented utilization of glucose relative to perfusion compared with values in normal myocardium.

In both reversibly and persistently dysfunctional myocardium, utilization of glucose normalized to relative perfusion was markedly variable. No significant differences between the two types of myocardium were evident. In 5 of 24 dysfunctional but viable segments, myocardial utilization of glucose was >2 SD below the mean ^{18}F-fluorodeoxyglucose activity exhibited by normal myocardium (regional ^{18}F-fluorodeoxyglucose activity in these five dysfunctional segments averaged 66% of that of normal myocardium). None of these five segments exhibited augmented myocardial utilization of glucose normalized to perfusion. In contrast,

Table 2. Myocardial Perfusion and Metabolism Before and After Revascularization

Myocardial Segment	RMBF (% of peak)	k_1 (min^{-1})	FDG Activity (% of peak)	FDG/RMBF
Before Revascularization (16 patients)				
Normal (n=42)	[illegible] ± 13.2	0.064 ± 0.015	88.3 ± 11.1	1.04 ± 0.24
Viable (n=24)	69.2 ± 22.5*	0.061 ± 0.014	78.7 ± 14.4*	1.24 ± 0.41*
Nonviable (n=29)	63.9 ± 25.4*	0.042 ± 0.013*†	70.8 ± 18.6*	1.33 ± 0.85
After Revascularization (11 patients)				
Normal (n=29)	85.7 ± 12.7	0.066 ± 0.012	90.1 ± 10.6	1.07 ± 0.22
Viable (n=16)	85.1 ± 9.83‡	0.068 ± 0.024	83.1 ± 11.8	0.99 ± 0.18‡
Nonviable (n=22)	69.1 ± 20.7§‖	0.049 ± 0.021§	65.9 ± 18.1§‖	0.98 ± 0.19

*$p < 0.01$ compared with normal (before revascularization). †$p < 0.003$ compared with viable (before revascularization). ‡$p > 0.05$ compared with values before revascularization. §$p < 0.03$ compared with normal (after revascularization). ‖$p < 0.02$ compared with viable (after revascularization). Values are expressed as mean values ± SD. FDG = ^{18}F-fluorodeoxyglucose; k_1 = the rate constant describing myocardial clearance of ^{11}C-activity; RMBF = relative myocardial blood flow.

myocardial oxidative metabolism in these segments was similar (k_1 = 0.064 ± 0.024 min^{-1}) to that in the other dysfunctional but viable segments as judged from results of studies with ^{11}C-acetate.

The variability in the level of myocardial utilization of glucose normalized to flow exhibited by both types of dysfunctional myocardium is further typified by the results listed in Table 3. In 5 of 29 nonviable segments, relative myocardial utilization of glucose normalized to perfusion was increased, a pattern thought to be indicative of dysfunctional but viable myocardium. Indeed, the three highest ratios for relative utilization of glucose normalized to perfusion were evident in three of these segments. Nevertheless, in four of the five segments (including all three of the

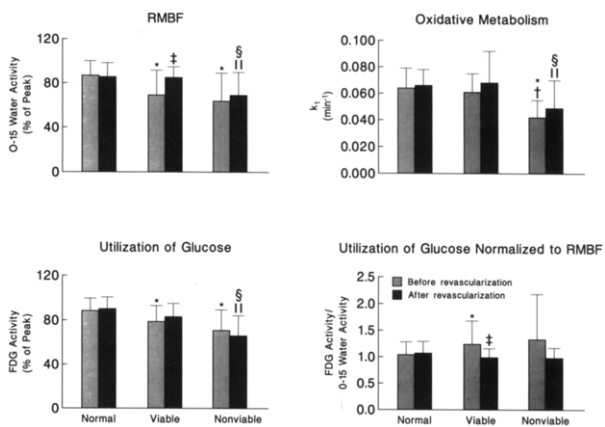

Figure 2. Histograms with average values (and standard deviations) for relative myocardial blood flow (RMBF), oxidative metabolism, utilization of glucose and utilization of glucose normalized to relative myocardial blood flow for segments containing normal, dysfunctional but viable and nonviable myocardium, both before and after coronary revascularization. Coronary revascularization had salutary effects on both myocardial blood flow and metabolism in segments containing dysfunctional but viable myocardium. Although after coronary revascularization, perfusion and metabolism tended to increase in segments containing nonviable myocardium, these segments still exhibited impaired perfusion and metabolism compared with both normal and dysfunctional but viable segments. *$p < 0.01$ compared with normal (before revascularization). †$p < 0.003$ compared with viable (before revascularization). ‡$p > 0.05$ compared with values before revascularization. §$p < 0.03$ compared with normal (after revascularization). ‖$p < 0.02$ compared with viable (after revascularization). Abbreviations as in Table 2.

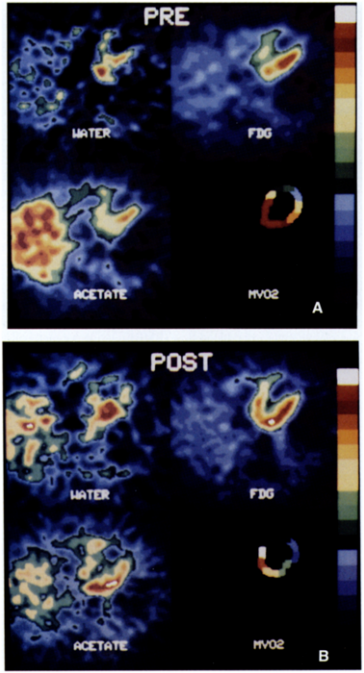

Figure 3. A, Tomographic reconstructions of myocardial perfusion and metabolism before (PRE) revascularization in the heart of Subject 9, who was subsequently found to have nonviable myocardium (as judged from wall motion analysis) in the anteroapical wall. The image of relative perfusion is at the **upper left** and that depicting relative glucose (FDG) utilization is at the **upper right**. The image at the **lower left** represents regional ^{11}C activity from 3 to 8 min after the administration of ^{11}C-acetate. At the **lower right** is a parametric display of relative values for k_1, reflecting regional differences in myocardial oxidative metabolism (MVO_2). **White** represents peak activity (or the fastest myocardial clearance of ^{11}C activity); **dark blue** represents lowest activity (or the slowest myocardial clearance of ^{11}C-activity). In the images the septum is to the left and anterior structures are superior. Before revascularization, myocardial perfusion and utilization of glucose were reduced concordantly within the anteroapical wall compared with values in the functionally normal posterolateral wall. Myocardial oxidative metabolism within the anteroapical wall was severely depressed 30% to 40% of that in the normal posterolateral wall. **B,** After (POST) revascularization, regional myocardial perfusion and glucose and oxidative metabolism within the anteroapical wall remained diminished compared with values in normal myocardium.

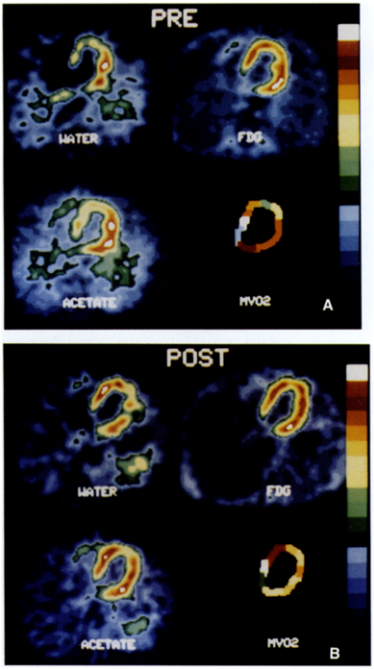

Figure 4. A, Reconstructions of myocardial perfusion and metabolism before (PRE) coronary revascularization in the heart of Subject 12, who was subsequently found to have viable myocardium in the anterior wall. Before revascularization, utilization of glucose (FDG) in the anterior wall was equivalent to that in the normal posterolateral wall despite the presence of mild anterior wall hypoperfusion. Although myocardial oxygen consumption (MVO_2) in the anterior wall was decreased relative to that in the normal posterolateral wall, the magnitude of the reduction is less than that in Figure 3. **B,** After (POST) revascularization, values for regional myocardial perfusion, utilization of glucose and oxidative metabolism in the anterior wall were comparable to values in normal myocardium.

segments with the highest values of utilization of glucose normalized to perfusion), myocardial oxidative metabolism was lower than that in any of the viable segments, demonstrating increased utilization of glucose relative to flow.

Estimates of perfusion and metabolism after revascularization. After coronary revascularization, both perfusion and metabolism improved in dysfunctional but viable myocar-

Table 3. Perfusion and Metabolism Before Revascularization in Dysfunctional Segments With Increased ^{18}F-fluorodeoxyglucose/Relative Myocardial Blood Flow*

Subject No.	Segments	RMBF (% of peak)	k_1 (min^{-1})	FDG Activity (% of peak)	FDG/RMBF
		Viable Myocardial Segments			
7	Septum	26.0	0.070	66.9	2.54
8	Posterolateral	59.1	0.064	96.9	1.64
11	Lateral	55.3	0.077	98.4	1.78
15	Apical	23.9	0.043	48.8	2.04
		Nonviable Myocardial Segments			
2	Posterolateral	26.2	0.033	79.4	3.03
	Inferior	22.2	0.032	100	4.50
11	Posterolateral	34.8	0.035	55.6	1.60
	Inferior	17.2	0.026	49.6	2.88
13	Septum	55.5	0.049	90.3	1.63

*Defined as >1.52 (normal mean ± 2 SD; see Table 2). Abbreviations as in Table 2.

dium (Table 2, Fig. 2 and 4). Regional perfusion increased to 85 ± 10% and regional utilization of glucose normalized to perfusion decreased to 1.0 ± 0.2, both of which were comparable to values in normal myocardium ($p < 0.05$ vs. values before revascularization). Despite the tendency toward improved perfusion and metabolism (Table 2, Fig. 2 and 3), nonviable myocardium continued to exhibit impaired perfusion and metabolism compared with that in normal myocardium ($p < 0.03$ for perfusion, oxidative metabolism and metabolism of glucose) or in reversibly dysfunctional myocardium ($p < 0.02$ for perfusion, oxidative metabolism and metabolism of glucose).

Changes in perfusion and metabolism in both types of dysfunctional myocardium could not be attributed simply to changes in loading conditions. Heart rate, systolic blood pressure and rate-pressure product at the time of the tomographic studies performed before revascularization (76 ± 9 beats/min, 128 ± 23 mm Hg and 9,751 ± 2,207 beats/min·mm Hg) were similar to values after revascularization (73 ± 10 beats/min, 127 ± 23 mm Hg and 9,430 ± 2,781 beats/min·mm Hg; p = NS).

Discussion

Results of this study indicate that, among patients with left ventricular dysfunction attributable to chronic coronary artery disease who undergo either coronary artery bypass surgery or coronary angioplasty, the presence of maintained oxidative metabolism is a descriptor and probably a critical determinant of the potential for recovery of regional mechanical function. In addition, results indicate that restoration of nutritive perfusion in dysfunctional myocardium has salutary effects on myocardial metabolism that underlie improved function.

Myocardial metabolism in relation to function. Because metabolism of glucose (both anaerobic and aerobic) predominates in ischemic myocardium, positron emission tomography with ^{18}F-fluorodeoxyglucose has been proposed (2,3) as a means for differentiating viable from nonviable myocardium in patients with coronary artery disease. Results of previous studies (2,3) in patients with left ventricular dysfunction attributable to chronic coronary artery disease showed that the persistence of myocardial utilization of glucose identified those segments of dysfunctional myocardium that retained the capacity for recovery of systolic function after revascularization. Conversely, the absence of myocardial utilization of glucose in dysfunctional myocardial segments before revascularization was indicative of tissue that lacked the potential for recovery of function. However, the use of this approach underestimated tissue viability 15% to 25% of the time and overestimated the extent of viable myocardium in 8% to 22% of all cases (2,3). The discordance may be related to the relative nonspecificity of kinetics of myocardial ^{18}F-fluorodeoxyglucose that reflect only overall myocardial utilization of glucose (both aerobic and anaerobic). Consequently, positron emission tomography with ^{18}F-fluorodeoxyglucose may not be sufficient to delineate directly those metabolic processes required for restoration of myocardial contractility.

Under physiologic conditions, myocardial oxidative metabolism is a prerequisite for contractile function. Results of studies employing a variety of measurements of regional systolic function have demonstrated a close and direct correlation between myocardial oxygen consumption and cardiac work (4,5). Under conditions of ischemia and reperfusion, maintenance of oxidative metabolism appears to be an important metabolic determinant of the capacity for functional recovery. Taegtmeyer et al. (6) showed that in isolated rat hearts rendered ischemic, recovery of function was contingent on a return of oxidative metabolism. Similar observations were made by Buxton et al. (7), who noted that oxidative metabolism in dog hearts (measured with positron emission tomography and ^{11}C-acetate) increased during the 1st month after reperfusion in dysfunctional but viable

myocardium. Although oxidative metabolism in such segments was initially depressed (compared with that in normal myocardium), it was less depressed than oxidative metabolism in nonviable tissue.

The same investigators (7) showed that utilization of glucose (assessed with positron emission tomography and ^{18}F-fluorodeoxyglucose) in dysfunctional but viable myocardium varied with the interval of observation after the restoration of perfusion. Similar phenomena are present in patients with recent myocardial infarction. Using the same methodology as in the present study, we (8) showed that in patients with recent myocardial infarction (average 6 days) undergoing coronary revascularization, oxidative metabolism was significantly higher in dysfunctional but viable myocardium than in nonviable myocardium. In contrast, utilization of glucose normalized to flow was markedly variable. Our observations in the present study (Table 2, Fig. 2) indicate that maintenance of oxidative metabolism may be similarly important in identifying the capacity for recovery of contractile performance in the heart of patients with left ventricular dysfunction attributable to coronary syndromes of a more chronic nature.

Comparison with previous studies. On first inspection, our findings of similar increases in metabolism of glucose normalized to perfusion in the two types of dysfunctional myocardium would appear to be discordant with results of previous studies. As mentioned previously, the presence of increased metabolism of glucose normalized to flow was a metabolic pattern more typical of dysfunctional but viable myocardium than of nonviable myocardium (2,3). However, in these studies, the number of dysfunctional segments demonstrating this metabolic pattern rather than the magnitude of utilization of glucose normalized to flow was determined. Our data suggest that augmentation of myocardial utilization of glucose normalized to flow can be quite pronounced in nonviable myocardium and is associated with reduced oxidative metabolism (Table 3). These findings are consistent with augmentation of anaerobic glycolysis and the view that anaerobic glycolysis alone is insufficient to maintain viability in the setting of a prolonged ischemic insult. Moreover, 5 of 24 dysfunctional but viable segments exhibited marked reductions in regional ^{18}F-fluorodeoxyglucose activity (and thus, regional myocardial utilization of glucose), but no increase in the utilization of glucose normalized to perfusion. Oxidative metabolism in these segments was comparable to that in reversibly dysfunctional segments. Thus, alternative substrates (such as free fatty acids) must have been utilized to support sustained oxidative metabolism. These results, taken in sum with similar observations in patients with recent myocardial infarction (8), suggest that criteria to predict functional recovery based on measurements of myocardial oxidative metabolism will compare favorably with those based on estimates of myocardial utilization of glucose.

Restoration of nutritive perfusion in dysfunctional but viable myocardium exerted salutary effects on both metabolism and mechanical performance. These findings are consistent with those of Tamaki et al. (3), who demonstrated that in patients with left ventricular dysfunction attributable to chronic coronary artery disease, improvement in mechanical performance after revascularization was accompanied by resolution of the augmentation in myocardial metabolism of glucose normalized to flow that had been observed before revascularization. In our study, nonviable myocardium tended to exhibit improved perfusion and metabolism after revascularization, although both perfusion and metabolism remained impaired compared with values in both normal myocardium and dysfunctional but viable myocardium (Table 2, Fig. 2). This tendency toward improvement may reflect nonischemic dysfunction or "stenting" of metabolically and functionally normal subepicardium by subjacent metabolically and functionally impaired subendocardium (19), the presence of pockets of metabolically active tissue interspersed with predominantly necrotic tissue, or both.

Methodologic considerations. Regional myocardial perfusion and utilization of glucose were measured in relative terms with respect to the regional distribution of ^{15}O and ^{18}F activities. Our group (20) and others (21) have validated the accuracy of positron emission tomography with $H_2{}^{15}O$ for the quantification of regional myocardial blood flow in absolute terms. However, in myocardium subjected to intense ischemia, quantitative estimates of perfusion are impaired by limited counting statistics, partial volume averaging and spillover effects. To acquire realistic estimates for such segments, we measured myocardial perfusion in relative terms by positron emission tomography with $H_2{}^{15}O$. This approach provides accurate estimates of regional perfusion, independent of the metabolic state of the tissue, over a wide range of flow rates, as judged from direct correlations with estimates of regional myocardial blood flow obtained with radiolabeled microspheres (12,13).

Recent results (22–24) have demonstrated that accurate quantitative estimates of overall myocardial utilization of glucose can be accomplished with positron emission tomography and ^{18}F-fluorodeoxyglucose when Patlak graphic analysis is employed. However, the accuracy of this approach for quantifying myocardial utilization of glucose has not been defined under conditions of severe ischemia and reperfusion in which the extent of dephosphorylation of ^{18}F-fluorodeoxyglucose-6-phosphate may vary. Significant dephosphorylation of ^{18}F-fluorodeoxyglucose-6-phosphate would result in the underestimation of overall myocardial utilization of glucose with the Patlak approach (22–24). Nevertheless, the regional distribution of myocardial ^{18}F-fluorodeoxyglucose activity 45 to 60 min after administration of tracer provides an accurate reflection of overall, regional myocardial utilization of glucose (25).

Strictly speaking, observations in this study are applicable only to patients who do not have diabetes mellitus. The myocardial kinetics of ^{18}F-fluorodeoxyglucose have not yet been fully elucidated in animals with experimentally induced diabetes mellitus or in patients with the disease. Although

results of preliminary studies indicate that myocardial images of ^{18}F-fluorodeoxyglucose activity of reasonable quality can be obtained in diabetic human subjects with protocols that tightly control the substrate environment, the clinical significance of patterns of regional myocardial accumulation of ^{18}F-fluorodeoxyglucose in these patients has yet to be determined (26). Myocardial clearance of ^{11}C activity (after the administration of ^{11}C-acetate) is relatively insensitive to changes in the substrate milieu (27). Consequently, the present observation that oxidative metabolism is an important descriptor of the capacity for functional recovery may be applicable in patients with diabetes mellitus.

Clinical implications. Our results indicate that in patients with left ventricular dysfunction attributable to chronic coronary artery disease, preservation of oxidative metabolism is a necessary condition for recovery of function. The presence of augmented myocardial utilization of glucose relative to perfusion identifies dysfunctional myocardium that retains the capacity for recovery of contractile performance only when the metabolic pattern reflects primarily oxidative utilization of glucose. The results indicate that measurement of myocardial oxygen consumption, as with positron emission tomography with ^{11}C-acetate, facilitates the accurate identification of those patients with left ventricular dysfunction who are likely to benefit from coronary revascularization.

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References

1. Gropler RJ, Bergmann SR. Myocardial viability. What is the definition? J Nucl Med 1991;32:10–2.
2. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. N Engl J Med 1986;314:884–8.
3. Tamaki N, Yonekura Y, Yamashita K, et al. Positron emission tomography using F-18-deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol 1989;64:860–5.
4. Sarnoff SJ, Braunwald E, Welch GH Jr, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 1958;192:148–56.
5. Graham TP Jr, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. J Clin Invest 1968;47:375–85.
6. Taegtmeyer H, Roberts AFC, Raine AEG. Energy metabolism in reperfused heart muscle: metabolic correlates to return of function. J Am Coll Cardiol 1985;6:864–70.
7. Buxton DB, Vaghaiwalla Mody F, Krivokapich J, Phelps ME, Schelbert H. Quantitative assessment of prolonged metabolic abnormalities in reperfused canine myocardium. Circulation 1992;85:1842–56.
8. Gropler RJ, Siegel BA, Sampathkumaran KS, et al. Dependence of recovery of contractile function on maintenance of oxidative metabolism after myocardial infarction. J Am Coll Cardiol 1992;19:989–97.
9. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
10. Ter-Pogossian MM, Ficke DC, Yamamoto M, Hood JT. Super PETT I: a positron emission tomograph utilizing photon time-of-flight information. IEEE Trans Med Imaging 1982;3:179–87.
11. Gropler RJ, Siegel BA, Lee KJ, et al. Non-uniformity of myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. J Nucl Med 1990;31:1749–56.
12. Bergmann SR, Fox KAA, Rand AL, et al. Quantification of regional myocardial blood flow in vivo with $H_2{}^{15}O$. Circulation 1984;70:724–33.
13. Knabb RM, Fox KAA, Sobel BE, Bergmann SR. Characterization of the functional significance of subcritical coronary stenoses with $H_2{}^{15}O$ and positron emission tomography. Circulation 1985;71:1271–8.
14. Walsh MN, Bergmann SR, Steele RL, et al. Delineation of impaired regional myocardial perfusion by positron emission tomography with $H_2{}^{15}O$. Circulation 1988;78:612–20.
15. Brown MA, Marshall DR, Sobel BE, Bergmann SR. Delineation of myocardial oxygen utilization with carbon-11-acetate. Circulation 1987; 76:687–96.
16. Armbrecht JJ, Buxton DB, Schelbert HR. Validation of [1-^{11}C]acetate as a tracer for noninvasive assessment of oxidative metabolism with positron emission tomography in normal, ischemic, postischemic, and hyperemic canine myocardium. Circulation 1989;81:1594–605.
17. Henes CG, Bergmann SR, Walsh MN, Sobel BE, Geltman EM. Assessment of myocardial oxidative metabolic reserve with positron emission tomography and carbon-11-acetate. J Nucl Med 1989;30:1489–99.
18. Marshall RC, Tillisch J, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, ^{18}F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation 1982;67:766–78.
19. Lima JAC, Becker LC, Melin JA, et al. Impaired thickening of nonischemic myocardium during acute regional ischemia in the dog. Circulation 1985;71:1048–59.
20. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. J Am Coll Cardiol 1989;14:639–52.
21. Iida H, Kanno I, Takahashi A, et al. Measurement of absolute myocardial blood flow with $H_2{}^{15}O$ and dynamic positron emission tomography: strategy for quantitation in relation to partial-volume effect. Circulation 1988;78:104–15.
22. Gambhir SS, Schwaiger M, Huang SC, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18-deoxyglucose. J Nucl Med 1989;30:359–66.
23. Choi Y, Hawkins RA, Huang S-C, et al. Parametric images of myocardial metabolic rate of glucose generated from dynamic cardiac PET and 2-[^{18}F]fluoro-2-deoxy-d-glucose studies. J Nucl Med 1991;32:733–8.
24. Hicks RJ, Herman WH, Kalff V, et al. Quantitative evaluation of regional substrate metabolism in the human heart by positron emission tomography. J Am Coll Cardiol 1991;18:101–11.
25. Ratib O, Phelps ME, Huang SC, Henze E, Selin CE, Schelbert HR. Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. J Nucl Med 1982;23:577–86.
26. Besozzi MC, Smith GT, Goodman MM, Buonocore E, Hubner KF. Improved clinical PET F-18-fluorodeoxyglucose (FDG) images in diabetics following i.v. insulin injections (abstr). J Nucl Med 1990;30:933.
27. Brown MA, Myears DW, Bergmann SR. Validity of estimates of myocardial oxidative metabolism with carbon-11-acetate and positron emission tomography despite altered patterns of substrate utilization. J Nucl Med 1989;30:187–93.